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CASE REPORT

Lung transplant survival despite unexpected pulmonary metastatic thyroid cancer in the explant

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Summary

A recent history of malignancy is considered by most transplant units as an absolute contraindication to transplantation. This particularly applies to the adult population, where the higher incidence of malignancy is related to age and exposure to relevant risk factors (e.g. smoking). In contrast, paediatric recipients are not extensively screened. Increasingly, children who develop chronic pulmonary graft-versus-host disease (GVHD) having survived treatment for haematological malignancies are being referred for lung transplantation. These patients do have a significant risk of secondary malignancy as a result of their underlying disease and/or prior treatments that need to be considered when being assessed for lung transplantation. We describe a 15- year-old patient who underwent cut-down lobar lung transplant for end-stage obliterative bronchiolitis secondary to GVHD that had developed as a result of haematopoietic stem cell transplantation for childhood acute lymphoblastic leukaemia. Unexpectedly, histopathological examination of the explant revealed extensive metastatic papillary thyroid cancer.

Case description

Our patient was a 15- year-old girl who underwent bilateral lung transplant in 2008 for presumed end-stage obliterative bronchiolitis (OB) related to chronic graft-versus-host disease (GVHD) secondary to haematopoietic stem cell transplantation (HSCT) for relapsed acute lymphoblastic leukaemia (ALL).

In 1995, aged 2 years, she was diagnosed with ALL (L1 type). Chemotherapy was commenced and haematological remission was maintained until 1997 when central nervous system and marrow relapse were noted. In June 1998, a mismatched sibling donor HSCT was performed. Conditioning included fractionated total body irradiation (TBI) of 12 Gy in total with craniocervical boost (6 Gy). In 2000, the patient developed transfusion-dependent anaemia. Bone marrow aspirate and trephine showed no evidence of relapse; however, engraftment studies showed mixed chimerism. Mini-allograft with CD34-selected peripheral blood progenitor cells from the same sibling donor was performed, followed by donor lymphocyte infusion. Complications included acute and chronic GVHD, predominantly affecting skin and lungs.

In 2001, in the setting of reduced exercise tolerance, cough and tachypnoea, an open lung biopsy was performed, confirming OB. Respiratory function testing showed a severe obstructive defect that failed to respond to high-dose corticosteroids, cyclosporine or methotrexate.

The patient was reviewed regularly and found to remain stable in terms of her respiratory, haematological and endocrine functions. In October 2007, aged 14 years, she was referred for lung transplantation. She was hypercapnic (PCO_2 66 mmHg), and respiratory function testing showed FEV_1 0.30 l (13% predicted) and FVC 0.6 l (27%). High resolution CT scan in February 2008, 6 months prior to transplant, showed mosaic attenuation consistent with air trapping secondary to OB with no

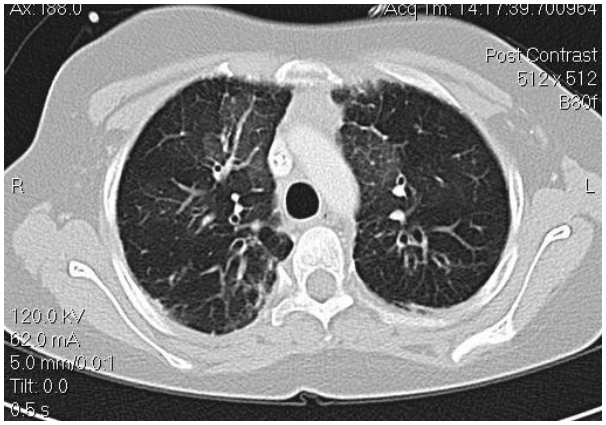

Figure 1 HRCT (8 February 2008) showing mosaic attenuation consistent with air trapping secondary to obliterative bronchiolitis. No evidence of metastatic papillary thyroid cancer.

other abnormality evident even in retrospect (Fig. 1). She was euthyroid (TSH 3.3 mU/l, T_4 14 pmol/l).

In August 2008, in the setting of accelerated clinical deterioration and progressive hypercapnic respiratory failure (PCO_2 111 mmHg), she underwent an uncomplicated cadaveric bilateral lobar transplant using lungs from an over-sized adult donor. Of note, 2 weeks prior to transplant, a neck ultrasound, performed to investigate suspected cervical lymphadenopathy, reported prominent lymphadenopathy within the neck, most likely related to reactive change. For reasons of the patient's precarious clinical state with progressive hypercapnia, this was not further investigated.

Unexpectedly, the explant histopathology demonstrated widespread metastatic papillary thyroid carcinoma on the background of OB (Fig. 2). Three weeks after lung transplant, total thyroidectomy and lymph node dissection were performed. Histology demonstrated a 35 -mm papillary thyroid carcinoma with extrathyroidal extension and lymph node involvement (Fig. 3). Radioactive iodine scan showed avid tissue in the neck, but no distant metastases. She received a treatment dose of 50 mCi radioiodine and thyroxine was commenced to suppress TSH (T_4 23.7 pmol/l, TSH <0.01 mU/l). Thyroglobulin remained detectable at 23.7 μg/l.

With regard to the lung allograft, there was no evidence of acute rejection on routine bronchoscopy at weeks 2, 4, 8 and 12. Respiratory function has remained stable with FEV_1 1.51 l (71%). As of February 2010, 17 months post-transplant, the patient was well and asymptomatic on standard immunosuppression of tacrolimus, azathioprine and prednisolone. Ongoing endocrine review continues and thyroglobulin has remained elevated at 17 μg/l.

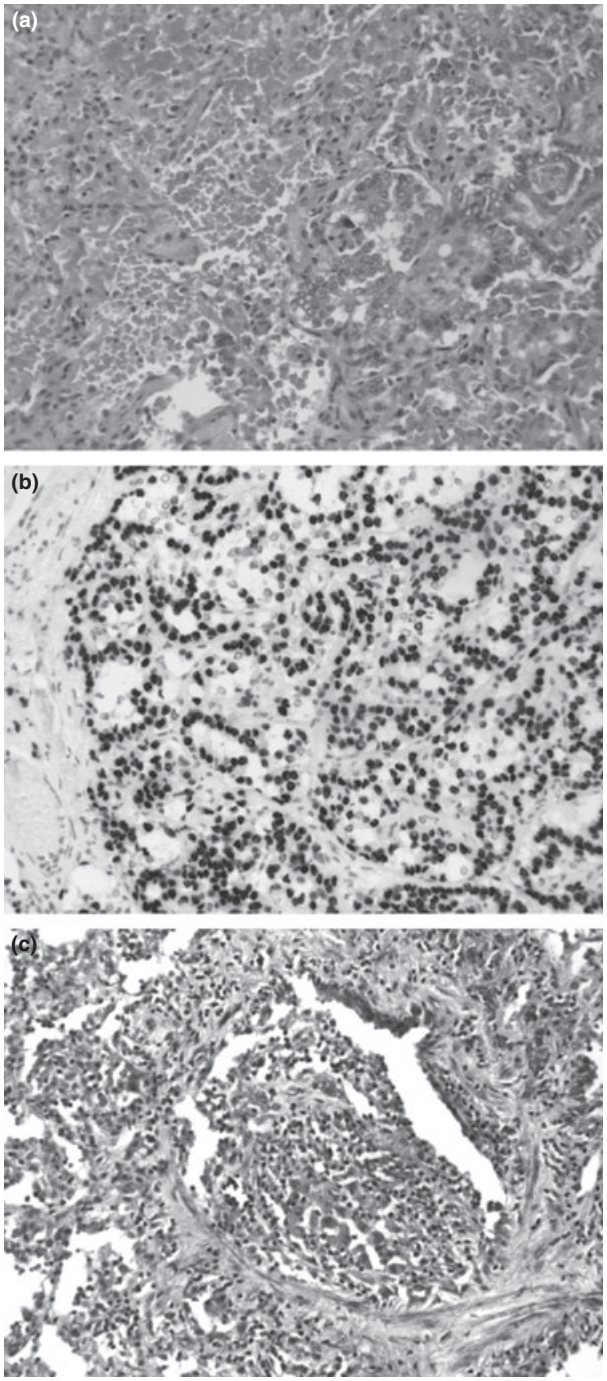

Figure 2 (a) Explant lung showing metastatic papillary thyroid carcinoma. H and E ×200 magnification. (b) Explant lung: thyroid transcription factor (TTF, Novocastra 1/500) immunoperoxidase highlighted the strong immunoreactivity within the papillary cell nuclei, consistent with that expected for a metastatic papillary thyroid carcinoma. (c) Explant lung showing obliterative bronchiolitis (Masson ×200 magnification).

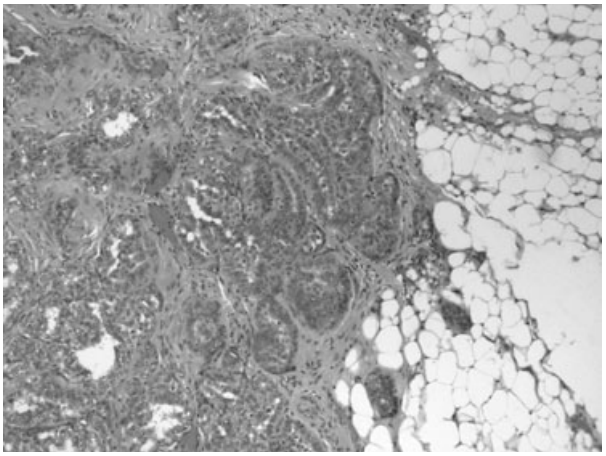

Figure 3 Thyroid gland: thyroid papillary carcinoma infiltrating fatty tissue in excision specimen (H and E ×200).

Discussion

Haematopoietic stem cell transplantation is a successful treatment for a number of haematological malignancies, solid tumours and some nonmalignant diseases [1]. It is, however, associated with a number of early and late complications affecting different organs.

Obliterative bronchiolitis is the most common, late noninfectious pulmonary complication following HSCT [2]. It is characterized by onset of new airflow obstruction and is most strongly associated with chronic GVHD [3]. Our patient fulfilled the criteria of the NIH consensus group for diagnosis of OB secondary to HSCT with documented airflow obstruction, histopathological confirmation and absence of infection[4]. Prognosis for such patients is poor with 35% mortality 3 years postdiagnosis [5]. Although her clinical deterioration was attributed to progressive OB, this was probably contributed to by the development of metastatic disease within the lungs. Retrospective analysis of CT imagery and thyroid function testing showed no abnormalities suggesting metastatic thyroid disease. Significantly, had such abnormalities been detected, the patient would not have been accepted by our programme and would not have proceeded to transplantation.

Despite a number of studies describing the increased risk of second solid tumour following HSCT[6], only a limited number of secondary thyroid cancers (STC) have been reported. A recent study by the European Bone Marrow Transplant Late Effects Working Party retrospectively reviewed 68 936 patients who had received HSCT identifying only 32 instances of STC [7]. The standardized incidence ratio of development of STC in this population was 3.26 when compared with age-matched controls, with the greatest risk factors being young age at transplant [relative risk (RR) 24.61 for those <10 years], irradiation (RR 3.44), female gender (RR 2.79) and chronic GVHD (RR 2.94).

Our patient underwent HSCT at age 5 and received TBI and craniocervical boost of 12 and 6 Gy respectively. External radiation, especially during childhood, has been associated with excess relative risk of thyroid cancer [8]; in addition, a number of studies have reported increased risk following TBI [9].

Despite increased risk of STC in patients after HSCT, it remains an uncommon late complication and as such, no consensus protocols exist with relation to follow-up screening. In more than 50% of reported cases of STC, thyroid function testing was normal and diagnosis was based on detection of palpable thyroid nodule or on neck ultrasound [7]. Although a neck ultrasound prior to transplantation did not reveal a thyroid mass, a more detailed departmental study post-transplant did identify a large nodule occupying most of the right lobe of the thyroid and three masses in the anterior triangle of the neck suspicious of metastatic lymphadenopathy.

Standard treatment of STC includes thyroidectomy and radioablative iodine. Overall survival is similar to that of primary papillary cancer with a 95% 5-year survival [10]. Follow-up includes monitoring of thyroglobulin and neck ultrasound. Our patient's persistent elevation of thyroglobulin (17 μg/l) and probable residual tissue in the right thyroid bed suggests residual disease. She is currently being managed with thyroxine to suppress TSH and further I^{131} ablation is planned for the future.

Traditionally, paediatric solid organ transplant recipients are not screened extensively for malignancy – a decision presumably based primarily on the age of the recipient and limited exposure to conventional risk factors, such as cigarette smoking. However, as illustrated by this case, the age of a transplant recipient is not the only mitigating factor in determining cancer risk. An increasing number of children who develop OB having survived treatment for haematological malignancies are being referred for lung transplantation. These patients do have a significant risk of secondary malignancy as a result of their underlying disease and/or prior treatments that need to be considered. The risk of secondary malignancy in this group is inversely related to age at the time of HSCT and children, who receive HSCT under 10 years old, have a reported risk of developing a secondary thyroid malignancy that is 24.61 times of that expected for age-matched controls [7] and an overall increased cumulative cancer risk of 11% at 15 years post-HSCT [9]. This increased risk is particularly attributed to the development of melanoma, cancer of the buccal cavity, brain, liver and thyroid cancer [1,9] and is higher in patients who have received irradiation as part of the preconditioning regime [11]. As such, this case emphasizes not only

the need for continued vigilance and reassessment of patients listed for lung transplantation [12], particularly with regard to the potential complications of the underlying disease and/or prior treatments but also the need for the development of consensus protocols with regard to the screening for malignancy in the paediatric population. We would suggest that all potential paediatric transplant recipients who have previously received HSCT and in particular, those who have undergone irradiation during preconditioning, should be screened for malignancy prior to listing for transplantation.

Authorship

Miranda Paraskeva: wrote the manuscript, collected and analysed data. Catriona McLean: analysed histopathology. Gregory Snell: wrote the manuscript. Glen Westall: wrote the manuscript.

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